REMARKS

Claims 1-4 and 6-50 were pending. Claims 36-50 were withdrawn from consideration, and claim 5 was canceled. By virtue of this response, claims 1 and 18 have been amended, and claim 2 is cancelled. Support for the amendment of claim 1 is found in the specification on, *inter alia*, page 5, lines 10-15; and page 20, lines 17-24; and original claim 2. Accordingly, claims 1, 3, 4, 6-35 are under consideration.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover has not acquiesced to any rejections and/or objections made by the Patent Office. Applicant expressly reserves the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicant has carefully considered the points raised in the Final Office Action and believes that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Allowable Subject Matter

Applicant acknowledges with appreciation that the Examiner states that claim 7 appears to be allowable over the prior art of record but it is objected to for depending upon a rejected claim.

Restriction Requirement

Applicant acknowledges with appreciation that the Examiner has withdrawn restriction requirement previously presented of Groups I-LXII.

The Examiner states that this application contains claims 36-50 drawn to inventions non-elected without traverse and a complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144). Applicant will address this issue when other rejections are withdrawn.

Information Disclosure Statement

Applicant thanks the Examiner for having considered the Information Disclosure Statements submitted on 6/14/04 and 2/6/04, and references 65 and 128 of the Information Disclosure Statement submitted on 12/30/02.

Claim Objections

The Examiner objects to claim 18 for the recitation of "wherein the SAH is contacted with the mutant SAH hydrolase". The Examiner states that claim 1 refers to a method for assaying Hcy, SAH or adenosine in a sample wherein the sample is contacted with the hydrolase, and wherein the sample contains or is suspected to contain SAH, there is no specific step in claim 1 wherein SAH in the sample is isolated such that it can be contacted with the hydrolase as recited in claim 18. The Examiner suggests claim 18 be amended to recite "wherein the sample is contacted with the mutant..." for clarity and consistency.

Applicant respectfully notes that claim 18 has been amended as suggested by the Examiner. Applicant respectfully requests the objection be withdrawn.

Rejections under 35 U.S.C. §112, second paragraph

Applicant acknowledges with appreciation that the Examiner has withdrawn the rejection to claims 1-4 and 6-32 for the recitation of "catalytic activity". However, the Examiner maintains rejection to claim 2 for allegedly being indefinite for the recitation of the term "amino

acid directly involved in the SAH hydrolase's catalytic activity". The Examiner states that the specification at page 20 does not provide a definition or clarification as to what is encompassed by the term "directly involved" as it relates to catalytic activity. The Examiner further states that the section of the specification indicated by Applicant refers to 20 amino acids which interact with the substrate inhibitor and co-enzyme NAD+ in the x-ray crystal structure of the human SAH hydrolase in complex with a substrate analog inhibitor, and how one of skill in the art can make mutations of residues involved in substrate binding and catalysis. The Examiner also states that it does not indicate if it encompasses both (1) residues which if mutated eliminate catalytic activity, and (2) residues which if mutated may alter catalytic activity (i.e. reduction or increase).

Without acquiescence to the rejection, Applicant notes that claim 2 is cancelled and claim 1 as amended recites "an amino acid residue that participates in catalysis or that is directly interacting with NAD^+, NADH, Hcy, SAH or adenosine." Applicant respectfully submits that claim 1 as amended is definite.

In view of the above, Applicant respectfully requests withdrawal of the rejection.

Rejections under 35 U.S.C. §112, first paragraph

Written Description

Claims 1-4, 6, 8-35 remain rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner states that the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant respectfully traverses this rejection.

The Examiner states that while the mutants described in the specification appear to have the functional characteristics recited in the claims, the specification fails to provide (1) the structural

elements common to all mammalian SAH hydrolases, and (2) the specific structural changes which can be made to any mammalian SAH hydrolase such that they display the functional characteristics required. The Examiner further states that while it appears that several rat, one mouse and two human SAH hydrolases are known, and it is suggested that these enzymes are highly conserved during evolution, it is unclear as to how the disclosure of the structure of these species of the mammalian genus is sufficient to predict the structure of any mammalian SAH hydrolase if nothing is known as to how much structural conservation (i.e. % structural homology) is common among all the members of the genus and which are the structural elements most likely to be conserved.

Applicant disagrees with the Examiner. Applicant respectfully submits that the specification provides a functional characteristics coupled with a known or disclosed correlation between function and structure. As discussed in the previous response, amino acid sequences of SAH hydrolase are highly conserved among known mammalian species (for example, human and rat SAH hydrolase are identical at 97% amino acid residues). Even a *P. falciparum* SAH hydrolase is 70% homologous to C. elegans and 75% homologous to wheat and periwinkle sequences. See, page 16366 of Creedon et al., *J. Biol. Chem.* 269:16364-16370 (1994). In addition, amino acid residues that have been proposed to have roles in catalysis or substrate and coenzyme binding are identical for rat and human (Figure 2 of Creedon et al.), and the C-terminal regions of all known SAH hydrolase are extremely conserved and contain amino acid residues essential to the enzyme catalysis (specification, page 20, lines 15-24). Since amino acid residues that are directly interacting with and amino acid residues that are adjacent to amino acid residues that are directly interacting with the substrate and coenzyme are known for rat and human based on crystal structures of these two enzymes, and these amino acid residues that are directly or indirectly involved in catalytic activity and substrate and coenzyme binding are highly conserved among mammalian species, one skill in the art can mutate these residues in other mammalian species and obtain mutant mammalian SAH hydrolase having binding affinity for Hcy, SAH or adenosine but having

attenuated catalytic activity as claimed. Thus, the present claims are supported by structural features and by functional characteristics coupled with a known correlation between function and structure.

Applicant disagrees with the Examiner that the disclosure of the rat and human structure does not provide one of skill in the art with a clue as to which are the structural elements which are mostly likely to be variable in all the species of the genus and the role of that variability in SAH hydrolase activity or binding affinity. Applicant respectfully notes that the mutant SAH hydrolases of the present invention are generated by mutating amino acid residues that are involved directly or indirectly in the substrate and coenzyme binding and catalysis and these amino acid residues are highly conserved among the mammalian species known. As disclosed in the specification, SAH hydrolase from mammalian sources are homotetramer of approximate molecular weight of 180-190 kD and all these enzymes contain 4 molecules of tightly-bound NAD+ as a co-enzyme and include two consecutive reactions in the hydrolytic direction. See, page 20, lines 10-15. Based on current knowledge about mammalian SAH hydrolase, there is no indication that those unknown mammalian species would not have similar structures to the known species. Thus, the Examiner has not provided any reasonable basis for the argument that the correlation for the known species could not be applied to the unknown mammalian species.

The Examiner alleges that it is unclear as to how the species disclosed would be representative of any human SAH hydrolase, let alone all mammalian SAH hydrolase. Applicant disagrees with the Examiner. As discussed in the previous response, the specification provides several mutant SAH hydrolases derived from the human SAH hydrolase (SEQ ID NO:1). These mutants were generated based on x-ray structure of the substrate binding site and coenzyme binding site of human SAH hydrolase. *See*, specification, page 30, lines 24-26. Since all known mammalian SAH hydrolases are highly conserved in sequence, have similar molecular weight, and catalyze the reaction with a same mechanism, one skilled in the art would be able to predict amino

acid residues that are involved directly or indirectly in catalysis and binding based on two known crystal structures of SAH hydrolase (human and rat). Thus, the examples of mutant SAH hydrolase generated provide a representative number of species for the genus.

Applicant reiterates that the references cited (Witkowski et al. and Seffernick et al.) by the Examiner do not support the Examiner's argument that the disclosure of a few species from human, mouse and rat is not deemed sufficient to adequately describe the entire mammalian genus in the absence of any knowledge or guidance as to a structure/function correlation which is applicable to all members of the genus. The Examiner has not provided a reasonable basis for supporting that the unpredictability of the art related to other enzymes may be applied to SAH hydrolase. The structure homology of the present application is between mammalian SAH hydrolase which are known to catalyze the same reaction. One skilled in the art could derive mutant SAH hydrolase based on the sequence homology and known amino acid residues that are involved directly and indirectly in the catalytic activity and binding activity. Applicant also reiterates that generating mutant SAH hydrolase having the claimed characteristics only requires attenuating catalytic activity of the enzyme but maintain binding activity of the enzyme, and does not require any change of enzymatic functionality.

In view of the above, Applicant respectfully submits that the written description requirement has been met, and withdrawal of this rejection is respectfully requested.

Enablement

Claims 1-4, 6, 8-35 remain rejected under 35 U.S.C. §112, first paragraph, for allegedly not reasonably providing enablement for (1) a method for assaying Hcy, SAH, or adenosine using any mammalian-derived mutant SAH hydrolase having the functional characteristics recited in the claims, (2) the method of (1) further comprising detecting cholesterol and/or folic acid in the sample by any means, or (3) the method of (1) further comprising detecting cholesterol and/or folic acid in

a sample by any means, wherein the mutant SAH hydrolase comprises SEQ ID NO: 1 and also comprises the amino acid substitutions recited in claim 7 or in the specification.

Applicant respectfully traverses this rejection.

The Examiner contends that although the specification provides several mutants of a single mammalian SAH hydrolase which display the desired characteristics and the structure/function correlation found in regards to the human and rat SAH hydrolase may be applicable to some of the species in the genus, there is no teaching in the specification or the art regarding the level of structural conservation found among all mammalian SAH hydrolase and a correlation between structure and function for all the species in the genus. Applicant disagrees with the Examiner. Applicant respectfully reiterates that "patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991). MPEP §2164.02 provides that "[f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation." MPEP §2164.02 also provides "[p]roof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation." As discussed above and in the previous response, SAH hydrolase is highly conserved during evolution (a rat SAH hydrolase amino acid sequence is 97% identical to the human SAH hydrolase); even a *Plasmodium* malarial parasite SAH hydrolase amino acid sequence exhibits 75% similarity to the wheat and periwinkle sequence. *See*, Creedon et al.

The Examiner has not provided any reasonable basis for the argument that the working examples are not representative to the genus. *See* MPEP 2164.05 ("The examiner should never make the determination based on personal opinion. The determination should always be on the

weight of all of the evidence."(emphasis included)). Applicant respectfully requests that if the Examiner's rejection is based on facts within his or her personal knowledge, the Examiner will support this rejection with those facts in an affidavit by the Examiner according to MPEP § 2144.03. According to MPEP § 2144.03:

> When a rejection is based on facts within the personal knowledge of the examiner, the data should be stated as specifically as possible, and the facts must be supported, when called for by the applicant, by an affidavit from the examiner.

In addition, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. *See*, MPEP §2164.08(b). MPEP §2164.08(b) also provides that "[t]he standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more than effort than is normally required in the art." Applicant respectfully submits since the specification provides ample teachings and guidance for generating mutant SAH hydrolase and testing activities of the mutants which are routine experimentation, the possibility of inoperative embodiments present within the scope of the pending claims does not render the pending claims nonenabled.

The Examiner contends that in the instant case, what is disclosed in the specification and what is known in the prior art does not prevent undue experimentation. The Examiner further contends that cloning and isolation of any mammalian SAH hydrolase wherein the SAH hydrolase shares very litter structural homology with what is known in the art would constitute undue experimentation, unless something is known about the structure of what is to be isolated. The Examiner states that even if cloning and isolation of any mammalian SAH hydrolase could be done without undue experimentation, the method requires mutants of mammalian SAH hydrolase wherein the mutants display specific functional characteristics.

Applicant disagrees with the Examiner. The Examiner has not provided any evidence of the presence of SAH hydrolase that shares very litter structural homology with what is known in the art among mammalian species in view of the conservation between *Plasmodium* malarial parasites and the wheat and periwinkle sequences. The specification teaches how to generate mutants of SAH hydrolase based on the amino acid residues that are directly interacting or adjacent to amino acid residues that are directly interacting with the substrate and coenzyme. Based on the conservation of these amino acid residues, one skilled in the art could apply the teachings of the specification to other species without undue experimentation. Again, if the Examiner's rejection is based on personal knowledge, the Examiner needs to submit an affidavit according to MPEP § 2144.03 to support the rejection.

With respect to the rejection to method for detection of cholesterol and/or folic acid, the Examiner states that it is noted that the method of claim 35 requires the use the same sample used to detect Hcy, SAH or adenosine for detection of cholesterol and/or folic acid, and as such, the sample will be treated using any means necessary to detect binding of Hcy, SAH or adenosine before it can be used to detect cholesterol and/or folic acid. The Examiner further states that one cannot reasonably conclude that the same methods known in the art for detection of cholesterol/folic acid would be effective in a sample which has been treated to detect Hcy, SAH or adenosine.

Applicant disagrees with the Examiner. Claim 35 does not have the limitation of performing cholesterol and/or folic acid after detecting binding of Hcy, SAH or adenosine. A sample may be split into two or more portions and different methods may be used for detecting different substances in the different portions.

In view of the above, Applicant respectfully submits that pending claims are enabled. Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

Rejections Under Nonstatutory Double Patenting

The Examiner maintains the rejection under the judicially created doctrine of obviousness-type double patenting to claims 1-3, 6, 8-9, 18-19, 23-24, 30-34 for alleged as being unpatentable over claims 1-3, 6-14, and 16 of U.S. Patent No. 6376210.

Applicant reiterates that this issue will be addressed when other rejections are withdrawn.

CONCLUSION

Applicant believes that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicant's representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no.466992000221.

Dated: December 9, 2004

Respectfully submitted,

By _____

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